CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-507

MEDICAL REVIEW

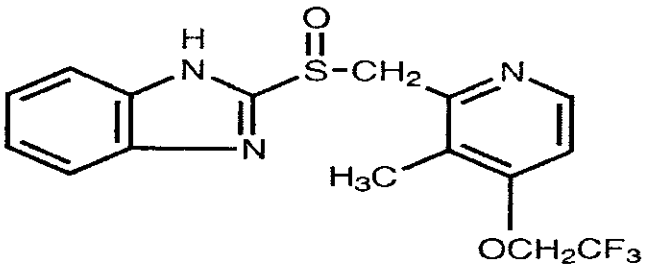
10/27/03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Gastrointestinal & Coagulation Drug Products
Medical Officer Review of NDA 21-507

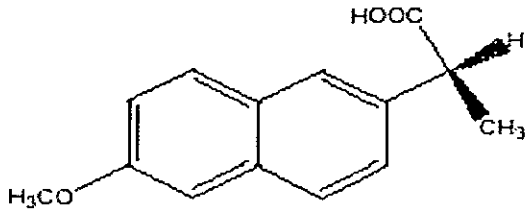
Date Submitted: July 24, 2003
Date Completed: October 22, 2003
Due Date: January 24, 2004

DRUG NAME: **Combination package containing Prevacid® (Lansoprazole) delayed-release oral capsules and Naprosyn® (Naproxen) oral tablets**

Proprietary Name:	Prevacid
Generic Name:	Lansoprazole
Chemical Name:	2-[[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methyl] sulfinyl] benzimidazole
Molecular Formula:	$C_{16}H_{14}F_3N_3O_2S$
Drug Class:	Substituted benzimidazole proton pump inhibitor
Chemical Structure:	



Proprietary Name:	Naprosyn
Generic Name:	Naproxen
Chemical Name:	(S)-6-methoxy-α -methyl-2-naphthaleneacetic acid.
Molecular Formula:	$C_{14}H_{14}O_3$
Drug Class:	Non-Steroidal Anti-Inflammatory Drug (NSAID)
Chemical Structure:	



THREE DOSES: 1) One 15 mg prevacid capsule per day and one 250 mg Naprosyn tablet BID
2) One 15 mg prevacid capsule per day and one 375 mg Naprosyn tablet BID
3) One 15 mg prevacid capsule per day and one 500 mg Naprosyn tablet BID

SPONSOR: TAP Pharmaceutical Products Inc., 675 North Field Dr., Lake Forest, IL 60015

INDICATION: Risk reduction of NSAID-associated gastric ulcers in adult patients – with a history of a documented gastric ulcer – who require the use of an NSAID.

BACKGROUND:

On September 6, 2002, the sponsor submitted NDA 21-507. On July 9, 2003, the Division of Gastrointestinal & Coagulation Drug Products took an approvable action on NDA 21-507 because of outstanding chemistry deficiencies.

On July 24, 2003, after correcting all outstanding chemistry issues, the sponsor submitted a complete response to the approvable letter. After reviewing the resubmission, the chemistry reviewer recommended approval.

RECOMMENDATIONS FOR REGULATORY ACTION:

Dr. Narayan Nair, a medical officer in the Division of Gastrointestinal & Coagulation Drug Products, performed a thorough clinical review of NDA 21-507. After evaluating Dr. Nair's review of NDA 21-507, I agree with his clinical review. Therefore, this medical officer recommends **approval** of the combination package containing **Prevacid® (Lansoprazole)** delayed-release oral capsules **and Naprosyn® (Naproxen)** oral tablets for the following indication: Risk reduction of NSAID-associated gastric ulcers in adult patients – with a history of a documented gastric ulcer – who require the use of an NSAID.

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/s/

Eric Brodsky
10/27/03 11:38:42 AM
MEDICAL OFFICER

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10/27/03 11:40:51 AM
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Robert Justice
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06/13/03

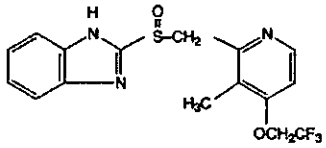
Medical Officer Review of NDA 21-507: New Combination Package Containing Prevacid® (Lansoprazole) Delayed-Release Capsules and Naprosyn® (Naproxen) Tablets

Date Submitted: 6 September 2002
Date Received: 11 September 2002
Date Assigned: 16 September 2002
Date Completed: 6 May 2003

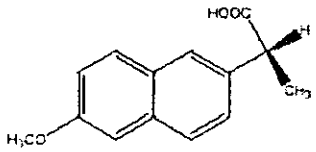
Applicant: TAP Pharmaceutical Products Inc.
675 North Field Drive
Lake Forest, IL 60015
Contact person: Doug Donovan

Drugs:

Proprietary Name - Prevacid
Generic Name - Lansoprazole
Chemical Name - 2-{[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole
Molecular formula - $C^{16}H^{14}F^3N^3O^2S$
Molecular structure -



Proprietary Name - Naprosyn
Generic Name - Naproxen
Chemical Name - (S)-6-methoxy-α -methyl-2-naphthaleneacetic acid.
Molecular formula - $C_{14}H_{14}0_3$
Molecular structure –



Drug Class: Substituted benzimidazole proton pump inhibitor
Non-Steroidal Anti-Inflammatory
Formulation: capsule and tablet

Route of Administration: Oral; 15 mg capsules and 250, 375 and 500 mg tablets

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Clinical Review for NDA 21-507

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This medical officer recommends approval of combination package containing two established and approved individual drug components, Prevacid Delayed-Release 15 mg capsules and either Naprosyn 250 mg, 375 mg or 500 mg tablets. TAP Pharmaceutical Products Inc. (TAP) has submitted an New Drug Application (NDA) for a combination package to be indicated for the risk reduction of NSAID (nonsteroidal anti-inflammatory drugs) -associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Lansoprazole is already approved for this indication (NDA 20-406/S-033), thus, this submission is in support of its combination packaging with naproxen tablets.

From a regulatory standpoint, this NDA is somewhat unique. The FDA has limited guidance pertaining to the co-packaging of drugs. 21 CFR 300.50 discusses the medical rationale for the regulation of combination drug products. This regulation states that drugs may be combined "to enhance the safety and effectiveness of the principle active component". However, no mention is made of co-packaging products. The Agency has developed a draft guidance on the co-packaging of drug, biologic and device products. This draft guidance states that a medical rationale should be provided by demonstrating the clinical usefulness of simultaneous use of the co-packaged drugs. The applicant fulfils these regulatory requirements by demonstrating that the safety of naproxen is enhanced by co-packaging with lansoprazole. Based on prospective data from the Arthritis Rheumatism and Aging Medical Information System, it is estimated that 13 of every 1000 patients with rheumatoid arthritis and 7.3 per 1000 patients with osteoarthritis who take NSAIDs for one year have a serious gastrointestinal complication. Given the vast number of patients on chronic NSAIDs, these complications result in an estimated 103,000 hospitalizations and annual expenditure of $2 billion. The applicant has demonstrated that lansoprazole enhances the safety of naproxen by reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who continue to take naproxen.

Support for approval of this NDA is based on an analysis of a subset of patients who were taking naproxen and lansoprazole in clinical study M95-301. In this study lansoprazole demonstrated a statistically significant risk reduction of NSAID-associated gastric ulcer compared to placebo. Safety of the co-packaged product is established by a combination of postmarketing data, previous clinical trials, and the analysis from the study M95-301. This data when taken together establishes safety for use of these medications jointly.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The applicant has not submitted a formal study to evaluate the interaction between naproxen and lansoprazole but instead has chosen to rely on a literature review involving drugs in the same class and extrapolate the results to these two medications. It should be noted that

naproxen is an over the counter medication and has a wide therapeutic window. It could be argued that co-packaging these two medications together requires a higher standard for evaluation of drug interactions. However there is no evidence to suspect an interaction between lansoprazole and naproxen.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The applicant submitted the single study M95-301 to support the indication of risk reduction of NSAID-associated gastric ulcers in subjects continuing to take their NSAIDs. This study was previously reviewed and judged adequate to support lansoprazole's approval for this indication (NDA 20-406/S-033). This application contains a subset analysis of M95-301 with patients who were on naproxen. This clinical trial was a randomized, double-blinded, placebo controlled trial to consisting of 537 patients on a variety of NSAIDs. In support of this combination package, the applicant has submitted an overall clinical summary containing a review of a subset of 119 (22%) patients who took naproxen. The applicant also provided a safety update from postmarketing data.

B. Efficacy

The applicant submitted a single study M95-301 to demonstrate efficacy. Study M95-301 was a double-blind, randomized, placebo-and active controlled clinical trial. The objective of the study was to compare the efficacy and safety of lansoprazole 15 mg QD and 30 mg QD with misoprostol 200 mcg QID and placebo in the prevention of gastric ulcers in patients continuing to take NSAIDs. Subjects had to have an endoscopically documented history of gastric ulcer or a healed gastric ulcer without any current gastric ulcer to enter the study. The control drug (misoprostol) is approved by the FDA at this dose for the indication of reducing the risk of NSAID-induced gastric ulcers in patients at high risk of complications from gastric ulcer. The primary efficacy endpoint for the prevention study was occurrence of gastric ulcer after 4, 8, and 12 weeks of treatment. The applicant defined occurrence as a gastric ulcer confirmed endoscopically after entering the double-blind treatment period. Time to ulcer occurrence also was a primary endpoint. There were two secondary endpoints:

- Daily summaries: Summaries of day and night abdominal pain and ——— use as recorded in patient diary during the entire 12- week treatment period (———. was the only antacid allowed).
- Symptom relief at the end of the double-blind treatment period: Changes in the severity of symptoms based on investigator interview from baseline to the double-blind treatment period.

The results for the subjects who were taking naproxen demonstrated that when the time to occurrence of gastric ulcer was compared between groups subjects in the lansoprazole 15 mg and 30 mg QD treatment groups remained free from gastric ulcer significantly longer than subjects in the placebo group ($p<0.001$). By Week 12, the percent of intent-to-treat subjects remaining free from gastric ulcer was as follows:

- 33% for the placebo group
- 83% for the misoprostol group
- 89% for the lansoprazole 15 mg group

- 83% for lansoprazole 30 mg group

No statistically significant differences were observed between the lansoprazole 15 mg and 30 mg QD treatment groups or between the lansoprazole 15 mg or 30 mg QD and misoprostol treatment groups.

In regards to secondary endpoints, 116 patients completed daily summaries (28 placebo, 27 misoprostol, 37 lansoprazole 15 mg, and 24 lansoprazole 30 mg). Review of this data demonstrated patients treated with lansoprazole experienced significantly less severe abdominal pain and a significantly smaller percentage of days with daytime and nighttime abdominal pain than misoprostol-treated patients. Patients in the 15 mg and 30 mg lansoprazole arms had less antacid use than misoprostol-treated subjects as well. No statically significant differences were seen in the secondary endpoints between the lansoprazole arms and placebo.

C. Safety

The applicant has demonstrated the safety of this combination package. Naproxen and lansoprazole are already approved as safe and efficacious. Naproxen is approved for over the counter use. Their combined use of naproxen and lansoprazole has already been approved in NDA 20-406/S-33. The combination of postmarketing data, previous clinically trials, and the analysis from the study M95-301 all combine to establish safety for this combination package.

There is extensive postmarketing experience with lansoprazole since its approval on November 1, 1997. The Adverse Event Reporting System (AERS) has collected data on all adverse event reports associated with lansoprazole that have been received by the Agency. This consists of 10,115 events. Of these 1,658 (16.4%) events involved concomitant use of NSAIDs. Naproxen use was reported in 32 (1.9%) of these 1,658 events. A review of these events reveals the adverse event profile for lansoprazole with concomitant use of an NSAID is similar to lansoprazole alone.

A safety review of the pivotal trial M95-301 uncovered no safety concerns. The trial consisted of a total of 119 naproxen-only subjects in the study (30 subjects received placebo, 28 subjects received misoprostol, 37 subjects received lansoprazole 15 mg, and 24 subjects received lansoprazole 30 mg). The duration of the study was 12 weeks. The mean duration of naproxen use among patients was between 19 to 27 months for each treatment group. The mean dosage ranged between 950 to 975 mg for the treatment groups. There were no significant differences among the four treatment groups with respect to the incidence of any treatment-emergent adverse event. The lansoprazole 15 mg group had statistically significantly fewer possibly or probably treatment-related adverse events reported compared to the misoprostol group ($p = 0.032$). Possibly or probably treatment related adverse events occurred in 5.4% of 37 subjects given lansoprazole 15 mg, 12.5% of 24 subjects given lansoprazole 30 mg, 25.0% of 28 subjects given misoprostol and 13.3% of 30 subjects given placebo. Only two of the 37 subjects given lansoprazole 15 mg had adverse events considered by individual investigators to be possibly or probably treatment-related (one case each of diarrhea and dry mouth). None of the adverse events that led to withdrawals were related to the study drug.

D. Dosing

The applicant is proposing a combination package of four 7-day blister cards containing two naproxen tablets (either 250 mg, 375 mg or 500 mg strengths) and 15 mg lansoprazole capsule. The naproxen is to be taken twice a day, and the lansoprazole is to be taken in the morning. The advantage of a combination package is it allows for a single prescription and this is purported to improve compliance although this has not been formerly studied. Patients who

may be less likely to remember to take medications individually may be more adherent if they are packaged together. Combination packaging has the disadvantage of limiting individual dose titration. However by including various doses with the lansoprazole 15 mg there may be some flexibility in dosing. Seventy-five percent of naproxen users take 500 mg BID and 90% of naproxen prescriptions are written for the 375 mg and 500 mg strengths. It should be noted that in the data submitted the there were few patients who took over 1000 mg of naproxen. Therefore, the labeling should reflect the lack of data to support the efficacy of lansoprazole when the dose of naproxen is greater than 1000 mg.

E. Special Populations

The applicant did not submit any new data regarding gender, race or age effects on safety or efficacy. The efficacy data from study M95-301 was analyzed by gender and there did not appear to be any difference in efficacy based on gender. There also was no significant differences in safety profile between male and female patients.

An analysis was performed comparing the efficacy of patients under 65 years of age to those over 65. This analysis showed that a higher proportion of lansoprazole patients of both age groups remained gastric ulcer-free by week 12 as compared to the placebo group. The safety data from study M95-301 did not reveal any issues particular to the geriatric population. There are no specific safety issues regarding lansoprazole use in the elderly. However, the clearance of lansoprazole is decreased in the geriatric population. The naproxen label relates no safety issues in the elderly. However it is well known that patients over the age of 60 years are at higher risk of gastrointestinal complications from NSAIDs.

Because of the relatively small numbers, a subgroup analysis with respect to race was not performed. The current lansoprazole label states that Asians have an increase in the AUC when compared to patients in the U.S. However, since the approval of lansoprazole no safety or efficacy differences in various ethnic subgroups have come to light. The current naproxen label does not relate any issues with regard to use in different races.

The applicant currently has no plans to pursue a pediatric indication. Chronic NSAID use and NSAID induced gastric ulcers are less common in the pediatric population. Due to the small numbers involved, there are currently no plans to request pediatric studies pertaining to this indication in the Agency's Written Request for proton pump inhibitors.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

TAP Pharmaceutical Products Inc. (TAP) has submitted a New Drug Application (NDA) in regards to a combination package containing two established and approved individual drug components, Prevacid Delayed-Release 15 mg capsules and either Naprosyn 250 mg, 375 mg or 500 mg tablets. The proposed trade name Is "NAPRAPAC". Prevacid (lansoprazole) Delayed-Release Capsules belong to the proton-pump inhibitor class of medications. Naprosyn (naproxen) tablets belong to the non-steroidal anti-inflammatory (NSAID) class of medication. The applicant's proposed indication is for "risk reduction of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID" Lansoprazole is already approved for this indication (NDA 20-406/S-033); thus, this submission is in support of its combination packaging with naproxen tablets. The proposed dose would be 15 mg of lansoprazole taken once a day and either 250 mg, 375 mg or 500 mg of naproxen taken twice a day. This combination package is intended for adult use since the safety and effectiveness in pediatric patients have not been established.

B. State of Armamentarium for Indication(s)

There are four other proton pump inhibitors approved for use in the United States. Currently none of the four has an indication for risk reduction in NSAID-associated gastric ulcers.

Misoprostol is a gastrointestinal mucosal protective prostaglandin E_1 analog that was approved December 27, 1988. It is indicated for reducing the risk of NSAID (including aspirin) induced gastric ulcers in patients at high risk of complications from gastric ulcer. Arthrotec is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol. It was approved December 24, 1997, and is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications.

C. Important Milestones in Product Development

Lansoprazole is a proton pump inhibitor and was initially approved by the FDA on May 10, 1995. It reduces the pH of the stomach by inhibition of the (H^+K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Lansoprazole is supplied in enteric coated capsules available in 15 mg and 30 mg strength and is approved for the following indications in adults:

- Short-term treatment of active duodenal ulcer
- *H. pylori* eradication
- Maintenance of healed duodenal ulcers
- Short-term treatment of active benign gastric ulcer
- Healing of NSAID-associated gastric ulcer
- Risk reduction of NSAID-associated gastric ulcer
- Gastroesophageal reflux disease (GERD)
- Maintenance of healing of erosive esophagitis

- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome

In July of 1999, TAP submitted Supplement 033 (S-033) to the original lansoprazole (Prevacid) New Drug Application 20-406 (NDA 20-406/S-033). This supplement presented the efficacy and safety of lansoprazole versus misoprostol or placebo in healing and risk reduction of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers. Both indications were approved on November 30, 2000.

On February 22, 2002, a Pre-NDA meeting was held between the Agency and TAP. At this meeting the applicant proposed convenience packs that were to contain lansoprazole capsules with naproxen. Several issues were discussed at this meeting such as stability information. The Agency requested any NDA submission contain information pertaining to the following issues:

- rationale for choosing what form of naproxen would be used
- form of naproxen to be used
- use of 7-day blister packs in patients who require chronic therapy
- individualization of naproxen dosage
- treatment of acute pain
- potential for lansoprazole to mask symptoms/signs of gastric ulcer
- drug-drug interactions.

TAP submitted the NDA on September 6, 2002. A 60-day filing meeting was held at the Agency and it was decided that the application was filable. However, it was decided that further clinical information was needed. In November 2002 the agency requested that TAP provide data on all the naproxen subjects in their studies in support of NDA 20-406/S-033 where they were approved for healing and reduction in risk of NSAID-associated ulcers. TAP provided the required information in December 2003.

D. Other Relevant Information

Lansoprazole is approved for use to treat adults with GERD in 105 countries in North and South America, Africa, Asia, and Europe. It has been marketed in the U.S. since 1995.

E. Important Issues with Pharmacologically Related Agents

NSAIDs are among the most commonly prescribed medications in the United States. However, they have been associated with sometimes fatal gastrointestinal bleeding. For this reason, there have been attempts to market drugs with the analgesic properties of NSAIDs but with a more favorable risk benefit profile. The combination product arthrotec containing diclofenac sodium (a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties), and misoprostol represents one of these attempts. The cyclooxygenase-2 (COX-2) inhibitors have a similar mechanism of action to NSAIDs but reportedly less GI side effects. However, the use of Cox-2 agents has come into question with potential linkage to increased cardiovascular risk and questions regarding true reduction of gastric complications..

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Dr. Dionne L. Price conducted the statistical review. In her review she states that she is in general agreement with the sponsor's statistical results and conclusions. She goes on to further state that the application contained statistical support favoring the co-packaged product in the

risk reduction of nonsteroidal anti-inflammatory drug (NSAID) associated gastric ulcers. She performed an analysis with respect to gender and age as well for the primary efficacy variable. This analysis showed that a higher percentage of patients treated with lansoprazole remained ulcer-free compared to placebo regardless of age or gender.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Lansoprazole inhibits gastric acid secretion by inhibiting the parietal cell membrane enzyme (H +, K +) –ATPase also known as the proton pump. Each capsule contains enteric coated granules. The drug is thus absorbed in the small intestine and enters the gastric parietal cells from the plasma. Lansoprazole binds covalently to the sulfhydryl groups on (H +, K +) -ATPase, causing prolonged inhibition of the proton pump.

Lansoprazole is metabolized in the liver into two major metabolites: 5-hydroxylansoprazole and lansoprazole sulfone. The 5-hydroxylation of lansoprazole is primarily catalyzed by CYP2C19, and the sulfoxidation of lansoprazole is primarily catalyzed by CYP3A4/5. One third of the lansoprazole is excreted as metabolites in the urine with virtually no unchanged parent drug detectable, and the remainder is excreted in the feces. The plasma half-life of lansoprazole is 1.5 hours, however the inhibition of the proton pump lasts much longer due to the covalent binding of the proton pump.

Naproxen is a member of the 2-arylpropionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is virtually completely absorbed from gastrointestinal tract with an oral bioavailability of 95%. The peak plasma concentration typically occurs 1 to 4 hours after ingestion. Greater than 99% of the naproxen is albumin-bound. Naproxen is extensively metabolized to O-desmethylnaproxen by the CYP isoforms CYP 2C9, and CYP 1A2, 2C8 to a lesser degree. Approximately 95% of the naproxen is excreted in urine, primarily as naproxen (less than 1%), O-desmethylnaproxen (less than 1%), or their conjugates (66% - 92%).

The applicant does not provide a formal study to evaluate the potential for drug-drug interaction between lansoprazole and naproxen but rather relies on literature review to support the conclusion that an interaction does not exist. Lansoprazole and naproxen are metabolized by different CYP isoforms – lansoprazole by 2C19 and 3A4 and naproxen by 2C9, 1A2, and 2C8. In general, proton pump inhibitors have few drug interactions at the CYP level. Clinical studies have demonstrated that lansoprazole does not have clinically significant interactions with other drugs metabolized by the CYP system, such as theophylline (1A2), caffeine (1A2), warfarin (2C9, 1A2, 3A4), phenytoin (2C9, 2C19), indomethacin (2C9), ibuprofen (2C9), diazepam (2C19), propranolol (2D6), prednisone (3A4), and antipyrine (1A2 and others). Several of these drugs share a metabolic pathway as naproxen with the same cytochrome P450 isoforms. However, *in vitro* data has shown that lansoprazole does induce CYP1A2 activity. Studies have not shown that this results in lower plasma concentration in drugs metabolized by this isozyme. The potential exists that lansoprazole may affect the absorption of naproxen by altering the stomach pH. The applicant cites a study in which omeprazole was co-administered with naproxen as well as other NSAIDs in healthy subjects. No change in absorption was seen. Another potential mechanism for interaction would be related to protein binding. Both naproxen and lansoprazole are highly protein bound in serum. Thus it is possible that one drug could displace the other and raise tissue concentrations. The applicant has not done a study to evaluate

this issue but does cite in vitro studies with other protein bound drugs and lansoprazole that demonstrate no such interaction.

Medical Officer Comments: *The lack of a formal study to evaluate the interaction between naproxen and lansoprazole may be a significant weakness in this submission. The applicant instead has chosen to rely on a literature review involving drugs in the same class and extrapolate the results to these two medications. It should be noted that naproxen is an over the counter medication and has a wide therapeutic window. .*

B. Pharmacodynamics

Naproxen has analgesic and anti-pyretic properties. It inhibits prostaglandin synthesis but the exact mechanism of action has not been delineated.

Lansoprazole suppresses gastric acid secretion by specific inhibition of the (H + ,K +)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This leads to inhibition of both basal and stimulated gastric acid secretion.

IV. Description of Clinical Data and Sources

A. Overall Data

This submission is a packaging NDA consisting primarily of CMC information and proposed labeling. TAP does provide, however, an overall clinical summary and an overall human pharmacokinetic summary. The review relies on data from NDA 20-406/S-033. This supplement presented the efficacy and safety of lansoprazole versus misoprostol or placebo in healing and risk reduction of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers. This review also utilized the literature reports cited by the applicant in support of this combination packaging.

B. Tables Listing the Clinical Trials

TABLE 1 – Clinical Trial in Support of NDA 21-507

STUDY NAME	DESIGN	# PATIENTS ENROLLED	DOSAGE	LOCATION
M95-301	Randomized, Double-blind, with active and placebo control	537 (119 took naproxen)	15 and 30 mg of Lansoprazole	63 centers in U.S. and Canada

C. Postmarketing Experience

Lansoprazole was approved November 1, 1997. The Adverse Event Reporting System (AERS) has collected data on all adverse events reports associated with lansoprazole that have been received by the Agency. This consists of 10,115 events. Of these 1,658 (16.4%) events involved concomitant use of NSAIDs. Naproxen use was reported in 32 (1.9%) of these 1,658 events. The following table displays the most commonly reported events.

TABLE 2- MOST FREQUENT (>1% OF REPORTED EVENTS) POSTMARKETING ADVERSE EVENTS

MedDRA PT Term	Lansoprazole Events=10,115	Lansoprazole with an NSAID Events=1,658
Diarrhea Nos	2.6%	2.5%
Condition Aggravated	2.1%	1.7%
Nausea	1.6%	1.7%
Pyrexia	1.5%	1.3%
Abdominal Pain Nos	1.3%	1.4%
Drug Interaction Nos	1.3%	1.2%
Dizziness (Excl Vertigo)	1.2%	1.3%
Headache Nos	1.1%	0.5%
Vomiting Nos	1.1%	1.3%
Dyspnea Nos	0.9%	1.0%

(Reference: Table 6.0a, Page 26)

Medical Officer Comments: *The number of case reports in which naproxen was a concomitant medication (32 patients) is too small to draw any conclusion. The adverse event profile for lansoprazole with concomitants use of an NSAID is similar to lansoprazole alone.*

C. Literature Review

The applicant submitted multiple references in support of this NDA. This consists of 11 articles from peer reviewed journals. Please see the appendix for a full listing.

V. Clinical Review Methods

A. How the Review was Conducted

The applicant's proposal for co-packaging is based on a single study M95-301. This study was reviewed in detail. In particular, close attention was placed on the subset of patients who took naproxen in this study.

B. Overview of Materials Consulted in Review

The review materials consisted of 9 volumes of printed material submitted by TAP. There was also full electronic submission that contained the safety and efficacy data as well as all the support documents.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

All case report forms and supplemental narratives were reviewed in detail for all subjects with serious adverse events. No discrepancy was found between the case report forms and the applicant's data. No DSI audit was done of the study sites since the study had been previously completed and led to approval of NDA 20-406/S-033.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was done within accepted ethical standards. It was conducted under the auspices of an Internal Review Board. Each patient signed a detailed informed consent, which explained the possible complications from participation in detail.

E. Evaluation of Financial Disclosure

Upon review of the financial disclosure by the investigators, there were no financial improprieties that would cast doubt on the findings of this study. None of the investigators listed by the applicant was on the FDA debarred list.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The applicant submitted the single study M95-301 to support the indication of risk reduction of NSAID-associated gastric ulcers in subjects continuing to take their NSAIDs. This study was previously reviewed and judged adequate to support 15 mg dose of lansoprazole being approved for this indication (NDA 20-406/S-033). This application contains a subset analysis of M95-301 with patients who were on naproxen. The subset analysis supports the efficacy of this combination package. Both doses of lansoprazole demonstrated a statistically significant risk reduction of NSAID-associated gastric ulcer compared to placebo. In addition, there was no statistical difference in risk reduction as compared to misoprostol in the naproxen-only subset.

B. General Approach to Review of the Efficacy of the Drug

TAP conducted a single clinical study entitled M95-301 in support of the indication of risk reduction of NSAID-associated gastric ulcers in subjects continuing to take their NSAIDs. This clinical trial was a randomized, double-blinded, placebo controlled trial to consisting of 537 patients on a variety of NSAIDs. The study was submitted in as part of NDA 20-406/S-033 and was initially reviewed by Dr. Sheldon Kress. M95-301 was deemed at that time sufficient to lead to approval for this indication. In support of this combination package, the applicant has submitted an overall clinical summary containing a review of a subset of 119 (22%) patients who took naproxen . After a filing meeting was held, the Agency requested further data pertaining to this subset of patients from study M95-301 to include :

- A breakdown of naproxen dosing
- Case report forms for naproxen patients
- Duration of naproxen exposure for patients
- Demographic information for naproxen patients
- Data sets for naproxen patients

For this medical review, Study M95-301 was reviewed in detail. The subset of patients who took naproxen was analyzed for efficacy utilizing both primary and secondary endpoints.

C. Detailed Review of Trials by Indication

1. Study Objectives and Endpoints

The objective of the study was to compare the efficacy and safety of lansoprazole 15 mg QD and 30 mg QD with misoprostol 200 mcg QID and placebo in the prevention of gastric ulcers in patients continuing to take NSAIDs.

The primary efficacy endpoint for the prevention study was occurrence of gastric ulcer after 4, 8, and 12 weeks of treatment. The applicant defined occurrence as a gastric ulcer confirmed endoscopically after entering the double-blind treatment period. Time to ulcer occurrence also was a primary endpoint. There were two secondary endpoints:

- Daily summaries: Summaries of day and night abdominal pain and Gelusil use as recorded in patient diary during the entire 12- week treatment period (Gelusil was the only antacid allowed).
- Symptom relief at the end of the double-blind treatment period: Changes in the severity of symptoms based on investigator interview from baseline to the double-blind treatment period.

2. Study Design and Methodology

Study M95-301 was a double-blind, randomized, placebo-and active controlled clinical trial. Subjects also had to have an endoscopically documented history of gastric ulcer or a healed gastric ulcer without any current gastric ulcer or no more than 25 gastric or duodenal erosions. The control drug is approved by the FDA at this dose for the indication of reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer. The study was designed to enroll 520 patients (130 patients in each treatment group) and to obtain 480 (120 evaluable patients in each treatment group). It was conducted in 63 sites in North America.

Screening Period (7 days duration)

During the screening period the following was performed

- Complete medical and social histories were documented.
- A complete physical examination
- Vital signs assessment
- Symptom assessment
- Laboratory evaluation
- Serology for *H. pylori*
- Endoscopy
- Rapid urease test
- Serum pregnancy test (for female patients)
- Gastric biopsy specimens were obtained for evaluation of gastritis and the presence of *H. pylori*

Treatment Period

The treatment period lasted 12 weeks. On Study Day 1, patients were randomly assigned in equal numbers to each of the four treatment groups. The lansoprazole and placebo was dispensed in a blinded fashion. The misoprostol was given open label but the endoscopist was blinded. Gelusil was dispensed at each visit to be taken as needed for relief of discomfort. NSAIDs were dispensed for those patients taking ibuprofen, piroxicam, naproxen, or diclofenac. Patients taking other NSAIDs were permitted to take their own supply. Patients returned to the study center at the end of Week 4, Week 8, and Week 12 for the following:

- Endoscopy
- Review of patient diaries
- Symptom assessment based on investigator interview
- Gastric biopsies

The double blind treatment period was discontinued in patients who developed a gastric or duodenal ulcer or erosive esophagitis during the 12 weeks. These patients were given the opportunity to receive treatment with lansoprazole 30 mg for 8 weeks given open label.

3. Eligibility Criteria

The following table displays the inclusion and exclusion criteria for this study.

TABLE 1 – ELIGIBILITY CRITERIA

Selection Criteria for Study M95-301	
Inclusion Criteria	**Exclusion Criteria**
Patient had an endoscopically-documented history of gastric ulcer with or without gastrointestinal bleed. Patients with a healed gastric ulcer in Studies M95-299 or M95-352 were also eligible. Patients with a previous history of coexisting gastric and duodenal ulcers were eligible.	Patient had evidence of gastric or duodenal ulcer crater or severe erosions (defined as ≥25 erosions) or erosive reflux esophagitis (defined as ≥ grade 2 according to the TAP grading scale [see Appendix 1] at the baseline endoscopy. Endoscopy must have been performed within 7 days prior to initiating study treatment.
Patient had been taking daily doses of an NSAID or aspirin ≥1300 mg/day for at least 4 Weeks prior to the Screening Visit. In addition, patients must have required chronic use of an NSAID for the next 12 weeks. Patients may have been treated with any NSAID (with the exception of nabumentone [Relafen®]) during the study, provided they took therapeutic dosages as recommended by the PDR®. The type and dose of NSAID was determined by the investigator.	Patient had evidence of active gastrointestinal bleeding at time of the Screening endoscopy.
Patient was *H. pylori* negative by CLO test, with subsequent confirmation by histology at Screening. Patients undergoing recent *H. pylori* eradication therapy were eligible, but must have waited a minimum of 4 weeks after conclusion of eradication therapy to be screened, with verification of successful eradication.	Patient had evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic, or endocrine disease or malignancy requiring active treatment (with the exception of basal cell carcinoma) or abnormality (other than the disease being studied). Patients with asymptomatic cholelithiasis or Gilbert's disease were eligible for participation.
Patients who required continuous treatment with digoxin, theophylline derivatives, and/or cyclosporin were eligible to enter the study, but must have had serum levels monitored during the study, to assure that proper levels of drugs were maintained.	Patient had laboratory, biochemical, and hematological parameters outside of normal limits or, if abnormal, judged clinically acceptable by the investigator. SGOT and SGPT must have been less than twice the upper limit of normal. Patients with elevated SGOT and SGPT values at the Screening Visit could not be rescreened. Also, serum creatinine must have been Z2 mg/dL.
Patients may have received chronic tricyclic antidepressant therapy, but may not have begun a new course of therapy or modify the dose after the start of the study.	Patient had evidence of alcohol abuse, illegal drug use, or drug abuse in the past 12 months.

Selection Criteria for Study M95-301 (cont'd)

Inclusion Criteria	Exclusion Criteria
Women of childbearing potential were excluded. Women must have been surgically sterile (tubal	Patient had a history of gastric, duodenal, or esophageal surgery (except for simple oversew of an

ligation, hysterectomy) or post-menopausal (defined as one year since last menstrual period) and had a negative pregnancy test.	ulcer).
Use of anti-ulcer medications, such as proton pump inhibitors, histamine H2-receptor antagonists' misoprostol, or antacids immediately prior to the Screening Visit were allowed. Proton pump inhibitors (Prilosec®, Prevacid®), histamine H2-receptor antagonists, and misoprostol must have been discontinued at least 24 hours prior to the first dose of study drug.	Patient required chronic anticoagulation therapy or treatment with Trental®, Ticlid®, or Fosamax®. Low-dose aspirin (Z325 mg/day) for cardiovascular indications only was acceptable during the study. Plaquenil® was allowed, but patients must not have required more than 400 mg/day.
Patients must have understood and been able to cooperate with study requirements. Patients must have signed and understood an informed consent prior to the screening procedures.	Patient took an investigational drug within 2 weeks (14 days) prior to initiating study treatment. Patient was treated with corticosteroids greater than the equivalent of 10 mg of prednisone per day.
	Patient had a history of hypersensitivity or allergic reaction to substituted benzimidazole compounds, prostaglandins, or the specified NSAID to be used in this study.

(Reference: Medical Officer Review NDA 20-406, pg. 61, Dr. Sheldon Kress)

Medical Officer Comment: *The inclusion and exclusion criteria were appropriate for this study.*

4. Statistical analysis

The protocol defined P-values less than or equal to 0.050 (when rounded to three digits) as significant. The difference between treatment groups in time to occurrence was compared using life table methodology. Subjects who withdrew from the study were assumed to have had occurrence at the same rates as those who remained in. Two additional prevention rates were calculated assuming that patients who withdrew prior to a visit using life table methods, 1) would have developed a gastric ulcer subsequent to withdrawal, or 2) would not have developed a gastric ulcer subsequent to withdrawal. Results were reported as percent of subjects with gastric ulcer occurrence (occurrence rates) or, alternatively, as percent of subjects free from gastric ulcer (ulcer-free rates). Cochran-Mantel-Haenszel methodology was used to compute P-values for comparing ulcer free or ulcer occurrence rates between treatment groups. The 12-week double-blind treatment period was divided in the following manner:
0 to 4 weeks (Study Days 0 to 28), 4 to 8 weeks (Study Days 29 to 56), and 8 to 12 weeks (Study Days 57 to 84).
For each time interval, subjects were evaluated as one of the following

- Not experiencing an occurrence during the interval - on the basis of an ulcer-free endoscopic evaluation after the midpoint of the interval
- Having experienced an occurrence during the interval
- Withdrawn as gastric ulcer free on the basis of an endoscopic evaluation before the midpoint of the interval.

A subject who withdrew after the midpoint of the interval was not considered as withdrawn for that interval, but was considered as withdrawn for the subsequent intervals.

Subjects recorded day and night abdominal pain, day and night joint pain, and Gelusil use in a diary daily. These were used to compute an average severity score per day during treatment in the following manner: a rating of 3 for severe, 2 for moderate, 1 for mild, and 0 for none. A Wilcoxon two-sample test was utilized to compare the average daily severity and percentage of

days with day and night abdominal pain and day and night joint pain/swelling during the entire 12-week treatment period. The Wilcoxon two-sample test was also used to compare the percentage of days Gelusil was used and the average number of Gelusil tablets used per day.

5. Results

Demographics

Total enrollment in the study consisted of 537 subjects (134 subjects randomized to receive placebo, 134 subjects randomized to receive misoprostol, 136 randomized to receive lansoprazole 15 mg, and 133 subjects randomized to receive lansoprazole 30 mg). The study was conducted at 63 centers throughout the U.S. and Canada. One-hundred nineteen subjects took only naproxen (with or without concomitant aspirin use) as their NSAID while on study (30 subjects received placebo, 28 received misoprostol, 37 received lansoprazole 15 mg, and 24 subjects received lansoprazole 30 mg).

The following table displays pertinent demographic information about the naproxen subset of patients.

TABLE 2 – SUMMARY OF DEMOGRAPHIC VARIABLES

SUMMARY OF DEMOGRAPHIC VARIABLES
FOR INTENT-TO-TREAT SUBJECTS WHO TOOK NAPROXEN ONLY OR
NAPROXEN AND ASPIRIN ONLY (M95-301)

VARIABLE	ALL SUBJECTS N= 119 n(%)	PLACEBO N= 30 n(%)	200 MCG QID MISOPROSTOL N= 28 n(%)	15 MG QD LANSOPRAZOLE N= 37 n(%)	30 MG QD LANSOPRAZOLE N= 24 n(%)	OVERALL P-VALUE@
GENDER						
FEMALE	73 (61.3)	19 (63.3)	19 (67.9)	21 (56.8)	14 (58.3)	
MALE	46 (38.7)	11 (36.7)	9 (32.1)	16 (43.2)	10 (41.7)	0.808
RACE						
CAUCASIAN	105 (88.2)	25 (83.3)	26 (92.9)	33 (89.2)	21 (87.5)	
BLACK	9 (7.6)	2 (6.7)	1 (3.6)	4 (10.8)	2 (8.3)	
OTHERS	5 (4.2)	3 (10.0)	1 (3.6)	0	1 (4.2)	0.506
TOBACCO USE						
TOBACCO NONUSER&	89 (74.8)	18 (60.0)	22 (78.6)	31 (83.8)	18 (75.0)	
TOBACCO USER	30 (25.2)	12 (40.0)	6 (21.4)	6 (16.2)	6 (25.0)	0.152
ALCOHOL USE						
NONDRINKER$	78 (65.5)	18 (60.0)	17 (60.7)	25 (67.6)	18 (75.0)	
DRINKER	41 (34.5)	12 (40.0)	11 (39.3)	12 (32.4)	6 (25.0)	0.633
CAFFEINE USE						
NO	16 (13.4)	2 (6.7)	5 (17.9)	6 (16.2)	3 (12.5)	
YES	102 (85.7)	28 (93.3)	23 (82.1)	31 (83.8)	20 (83.3)	0.596
PREVIOUS TREATMENT##						
LANSOPRAZOLE	33 (27.7)	12 (40.0)	7 (25.0)	7 (18.9)	7 (29.2)	
RANITIDINE	12 (10.1)	5 (16.7)	1 (3.6)	3 (8.1)	3 (12.5)	
NO PREVIOUS TREATMENT	74 (62.2)	13 (43.3)	20 (71.4)	27 (73.0)	14 (58.3)	0.213

& INCLUDES EX-TOBACCO USERS
$ INCLUDES EX-DRINKERS
TREATMENT TAKEN IMMEDIATELY BEFORE THE DOUBLE-BLIND TREATMENT PERIOD FOR SUBJECTS PREVIOUSLY ENROLLED IN STUDIES M95-299 OR M95-352
@ P-VALUE FROM CHI-SQUARE TEST; FOR ANALYSIS OF RACE, RACE CATEGORIES OTHER THAN CAUCASIAN AND BLACK ARE COMBINED INTO ONE CATEGORY

TABLE 2 – cont'd

SUMMARY OF DEMOGRAPHIC VARIABLES
FOR INTENT-TO-TREAT SUBJECTS WHO TOOK NAPROXEN ONLY OR
NAPROXEN AND ASPIRIN ONLY (M95-301)

VARIABLE	ALL SUBJECTS N=119	PLACEBO N= 30	200 MCG QID MISOPROSTOL N= 28	15 MG QD LANSOPRAZOLE N= 37	30 MG QD LANSOPRAZOLE N= 24	OVERALL P-VALUE@
AGE#:						
Number of patients	119	30	28	37	24	
Mean(SD) in years	59.5(11.3)	58.4(12.8)	56.9(9.9)	63.5(11.2)	57.7(10.0)	
Min-Max	37-84	39-84	39-80	39-80	37-74	0.072+
WEIGHT-MALES#:						
Number of patients	46	11	9	16	10	
Mean(SD) in lbs	212.0(36.7)	202.8(43.5)	216.4(34.5)	209.1(35.0)	222.8(35.8)	
Min-Max	138-299	138-261	174-299	156-280	160-283	0.631
WEIGHT-FEMALES#:						
Number of patients	73	19	19	21	14	
Mean(SD) in lbs	182.8(46.6)	199.9(45.0)	171.9(32.7)	185.2(60.3)	171.1(37.4)	
Min-Max	97-324	130-286	97-232	114-324	114-241	0.211
HEIGHT-MALES:						
Number of patients	45	11	8	16	10	
Mean(SD) in inches	70.2(2.9)	70.7(3.4)	69.6(2.2)	69.8(2.9)	70.6(2.8)	
Min-Max	65-78	65-76	67-72	67-78	65-75	0.766
HEIGHT-FEMALES:						
Number of patients	73	19	19	21	14	
Mean(SD) in inches	63.7(2.8)	64.4(2.9)	64.2(2.9)	63.5(2.3)	62.3(2.9)	
Min-Max	56-69	56-68	59-69	59-68	56-67	0.137

AT BASELINE
@ P-VALUE FROM F-TEST FOR TESTING EQUALITY OF TREATMENT MEANS
***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVELS, RESPECTIVELY

(Reference: Applicant electronic submission, Table 7 , page 28)

Medical Officer Comments: *The treatment groups were balanced with regard to most parameters. There were more female than male subjects for each treatment arm. There were fewer non-caffeine users in the placebo group. More subjects in the placebo arm had previous use of lansoprazole. These differences should not have affected outcome.*

The following table displays the dosage of naproxen that the subjects were taking.

TABLE 3 – DOSAGE OF NAPROXEN

DOSAGE OF NAPROXEN FOR INTENT-TO-TREAT SUBJECTS
WHO TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY
(M95-301)

	PLACEBO (N= 30)	MISOPROSTOL 200 MCG QID (N= 28)	LANSOPRAZOLE 15 MG QD (N= 37)	LANSOPRAZOLE 30 MG QD (N= 24)	P-VALUE#
HIGHEST TOTAL DAILY DOSE (MG) $					0.694
<750 MG/DAILY	2(6.7%)	0(0.0%)	4(10.8%)	1(4.2%)	
750-1000 MG/DAILY	26(86.7%)	25(89.3%)	31(83.8%)	23(95.8%)	
>1000 MG/DAILY	2(6.7%)	3(10.7%)	2(5.4%)	0(0.0%)	
MEAN(STD)	891.7(319.5)	950.0(238.8)	892.2(222.7)	875.0(180.6)	
MIN-MAX	500.0 - 2250.0	750.0 - 1600.0	500.0 - 1500.0	250.0 - 1000.0	

P-VALUE FOR F-TEST FOR TESTING EQUALITY OF TREATMENT MEANS

$ FOR SUBJECTS WHO CHANGED THE DOSE OF NAPROXEN TREATMENT, THE CALCULATION UTILIZED THE HIGHEST TOTAL DAILY DOSE EXPERIENCED.

(Reference: Applicant electronic submission, Table 1, page 1)

Medical Officer Comments: *The mean dose of naproxen was greatest in the misoprostol group and least in the lansoprazole 30 mg group. The lansoprazole 30 mg dose also had no subjects taking greater than 1000 mg of naproxen. Only 2 subjects (both in the lansoprazole 15 mg arm) were on a daily dose of naproxen greater than 1000 mg.*

The following table displays the duration of naproxen use for subjects enrolled in this study.

TABLE 4 – DURATION OF NAPROXEN USE

DURATION OF NAPROXEN FOR INTENT-TO-TREAT SUBJECTS
WHO TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY
(M95-301)

PLACEBO (N= 30)	MISOPROSTOL 200 MCG QID (N= 28)	LANSOPRAZOLE 15 MG QD (N= 37)	LANSOPRAZOLE 30 MG QD (N= 24)	P-VALUE**

TOTAL DURATION (MONTHS) *					0.890
<=6 MONTHS	13(43.3%)	18(64.3%)	13(35.1%)	11(45.8%)	
>6 MONTHS	17(56.7%)	10(35.7%)	24(64.9%)	13(54.2%)	
MEAN(STD)	23.7(34.4)	24.1(55.5)	19.4(21.8)	27.3(42.3)	
MIN-MAX	2.5 - 139.4	0.9 - 242.0	1.1 - 84.4	1.1 - 184.1	
DURATION PRIOR TO STUDY DRUG (MONTHS) *					0.887
<=6 MONTHS	18(60.0%)	19(67.9%)	16(43.2%)	14(58.3%)	
>6 MONTHS	12(40.0%)	9(32.1%)	21(56.8%)	10(41.7%)	
MEAN(STD)	21.0(34.7)	21.6(55.4)	16.7(21.9)	24.6(42.3)	
MIN-MAX	0.0 - 136.6	0.0 - 239.2	0.0 - 81.6	0.0 - 181.2	
DURATION DURING THE TREATMENT (MONTHS) *					0.678
<=2 MONTHS	6(20.0%)	5(17.9%)	4(10.8%)	2(8.3%)	
>2 MONTHS	24(80.0%)	23(82.1%)	33(89.2%)	22(91.7%)	
MEAN(STD)	2.7(1.1)	2.5(0.8)	2.8(0.6)	2.7(0.6)	
MIN-MAX	0.1 - 5.1	0.2 - 3.2	0.6 - 4.6	0.3 - 3.2	

* STUDY DRUG END DATE WAS USED FOR DURATION CALCULATION FOR SUBJECTS WHOSE NAPROXEN TREATMENT WAS ONGOING BEYOND STUDY DRUG END DATE
DURATIONS WERE COMBINED FOR SUBJECTS WHO CHANGED THE DOSE OF NAPROXEN TREATMENT
** P-VALUE FOR F-TEST FOR TESTING EQUALITY OF TREATMENT MEANS

(Reference: Applicant electronic submission, Table 2, page 2)

Medical Officer Comments: *The mean duration prior to the study drug was greatest in the lansoprazole 30 mg group. The mean duration prior to treatment was roughly equivalent in all treatment groups.*

Efficacy Results

The following table displays the primary efficacy endpoint - the gastric ulcer occurrence for naproxen only subjects.

TABLE 5 - GASTRIC ULCER OCCURRENCE STATUS FOR NAPROXEN-ONLY SUBJECTS IN STUDY M95-301

Treatment Group	Time Interval (weeks)		
	0-4	4-8	8-12
Naproxen-Only Subjects Intent-to-Treat Dataset			
Placebo (N=30)			
Occurrence	13	0	4
No Occurrence	14	13	7
Withdrawal	3	1	2
Misoprostol 200 µg QID (N=28)[a]			
Occurrence	3	0	1
No Occurrence	22	19	17
Withdrawal	3	3	1
Lansoprazole 15 mg QD (N=37)[a]			
Occurrence	3	1	0
No Occurrence	32	31	28
Withdrawal	2	0	3
Lansoprazole 30 mg QD (N=24)[a]			
Occurrence	4	0	0
No Occurrence	19	18	17
Withdrawal	1	1	1

[a] Statistically significant difference versus placebo group ($p \leq 0.05$).
Occurrence: endoscopic documentation of gastric ulcer associated with this time interval
No occurrence: endoscopic documentation of no gastric ulcer after the midpoint of interval
Withdrawal: no endoscopy available after midpoint of interval.
(Reference: Applicant electronic submission, Table 5.3a, page 85)

Medical Officer Comments: *Time to occurrence of gastric ulcer was compared between groups for naproxen-only subjects by life-table methodology. The results show subjects in the lansoprazole 15 mg and 30 mg QD treatment groups remained free from gastric ulcer significantly longer than subjects in the placebo group ($p<0.001$). There were no statistically significant differences seen between the lansoprazole 15 mg and 30 mg QD treatment groups nor between the lansoprazole 15 mg or 30 mg QD and misoprostol treatment groups.*

The following table displays the percentage of subjects that were gastric ulcer free at the end of the time interval.

TABLE 6 - PERCENTAGE OF NAPROXEN-ONLY SUBJECTS REMAINING GASTRIC ULCER FREE AT THE END OF THE TIME INTERVAL OF STUDY M95-301 CALCULATED BY LIFE-TABLE METHODOLOGY

	Time Interval (weeks)			95% Confidence Intervals	
Treatment Group	**0-4**	**4-8**	**8-12**	**At 4-8 Weeks**	**At 8-12 Weeks**
Naproxen-Only Subjects- Intent-to-Treat Dataset					
Placebo	52%	52%	33%	(33.0, 70.7)	(14.0, 52.0)
Misoprostol 200 µg QID	88%	88%	83%	(75.3, 100.0)	(67.9, 98.3)
Lansoprazole 15 mg QD	91%	89%	89%	(78.0, 99.1)	(78.0, 99.1)
Lansoprazole 30 mg QD	83%	83%	83%	(67.1, 98.1)	(67.1, 98.1)

(Reference: Applicant electronic submission, Table 5.3b, page 85)

The next table displays the percentage of subjects with gastric ulcer at the end of each time interval.

TABLE 7 - PERCENTAGE OF NAPROXEN-ONLY SUBJECTS WITH GASTRIC ULCER AT THE END OF THE TIME INTERVAL OF STUDY M95-301 CALCULATED BY LIFE-TABLE METHODOLOGY

	Time Interval (weeks)		
Treatment Group	**0-4**	**4-8**	**8-12**
Naproxen-Only Subjects- Intent-to-Treat Dataset			
Placebo	48%	48%	67%
Misoprostol 200 µg QID	12%	12%	17%
Lansoprazole 15 mg QD	9%	11%	11%
Lansoprazole 30 mg QD	17%	17%	17%

(Reference: Applicant electronic submission, Table 5.3c, page 86)

Medical Officer Comments: *Both lansoprazole arms demonstrated a risk reduction in the occurrence of gastric ulcers when compared to placebo. There was a statistically significant smaller percentage of subjects with gastric ulcer in the lansoprazole versus placebo. The misoprostol also demonstrated a risk reduction in gastric ulcers*

The following table displays diary data from the study.

TABLE 8 - DIARY RESULTS FOR NAPROXEN-ONLY SUBJECTS AT THE END OF THE 12-WEEK DOUBLE-BLIND TREATMENT PERIOD OF STUDY M95-301

	Treatment Group Mean			
Naproxen-Only Subjects Intent-to-Treat				
Variable	**Placebo (N=28)**	**Misoprostol 200 µµg QID (N=27)**	**Lansoprazole 15 mg QD (N=37)**	**Lansoprazole 30 mg QD (N=24)**
Daytime Abdominal Pain				
% of Days with Pain	28.5	48.3#	23.5*	28.0*
Average Pain Severity/Day	0.40	0.78	0.32	0.42
Nighttime Abdominal Pain				
% of Nights with Pain	24.3	39.3#	21.6*	22.7*
Average Pain Severity/Night	0.36	0.66	0.29	0.35
Gelusil Use				
Percent of Days Used	30.9	49.2#	21.1*	20.3*
Average Number/Day	0.99	1.76	0.57	0.58
Daytime Joint Pain/Swelling				
% of Days with Pain	58.2	51.3	47.3	55.4
Average Pain Severity/Day	0.95	0.91	0.84	0.82
Nighttime Joint Pain/Swelling				
% of Nights with Pain	56.6	51.4	45.2	53.5
Average Pain Severity/Night	0.89	0.92	0.79	0.76

Severity of pain: none = 0; mild = 1; moderate = 2; and severe = 3

* Statistically significant difference versus misoprostol treatment group ($p \leq 0.05$).

Statistically significant difference versus placebo group ($p \leq 0.05$).

(Reference: Applicant electronic submission, Table 5.3c, page 86)

Medical Officer Comments: *Subjects who were treated with lansoprazole demonstrated significantly less severe abdominal pain and a significantly smaller percentage of days with daytime and nights with nighttime abdominal pain than misoprostol-treated subjects. The subjects who took placebo experienced less severe abdominal pain and a smaller percentage of days with daytime and nighttime abdominal pain than misoprostol-treated subjects. This is somewhat unexpected. Previous trials involving misoprostol alone demonstrated abdominal pain occurring in 13-20% of patients but the number was no different than placebo. There was a significant difference seen for both the percent of days that Gelusil was used and for the average number of Gelusil tablets taken per day. There was less use of Gelusil reported by both groups of lansoprazole-treated subjects or placebo subjects than misoprostol-treated subjects. It is important to note that no statistically significant differences were observed between any of the treatment groups for the percentage of days or average pain severity of day or night joint pain/swelling for all subjects. This demonstrates that the lansoprazole did not appear to affect the efficacy of the naproxen.*

D. Efficacy Conclusions

Study M95-301 was previously reviewed and judged to demonstrate the efficacy of lansoprazole versus placebo in healing and risk reduction of NSAID-associated gastric ulcers while continuing NSAID treatment. In support of this combination package, TAP has submitted a subset analysis of naproxen only subjects. The results of this analysis demonstrates that lansoprazole is statistically significantly more effective than placebo in reducing the risk of NSAID-associated gastric ulcer in subjects who continue the use of NSAID therapy ($p \leq 0.001$). The results obtained in this subset analysis are comparable to that obtained in the overall trial containing subjects on a variety of NSAIDs. The results for Study M95-301 in all subjects at Week 12, demonstrate the percent of intent-to-treat subjects remaining free from gastric ulcer at Week 12 was 51%, 92%, 79%, and 83% in the placebo, misoprostol, lansoprazole 15 mg, and lansoprazole 30 mg groups, respectively. In the naproxen subset of patients by Week 12, the percent of intent-to-treat subjects remaining free from gastric ulcer was 33%, 83%, 89%, and 83% in the placebo, misoprostol, lansoprazole 15 mg, and lansoprazole 30 mg groups, respectively. Lansoprazole also demonstrated significantly less severe and a significantly smaller percentage of days with daytime and nights with nighttime abdominal pain than misoprostol-treated subjects. Patients in the lansoprazole arms had less use of antacids as well. In addition it does not appear that lansoprazole interfered with the efficacy of naproxen. There were no statistically significant differences observed among any of the treatment groups for the percentage of days or average pain severity of day or night joint pain/swelling.

However, some issues do remain regarding efficacy. There were too few subjects on high doses of naproxen (>1000 mg) to make firm conclusions about the efficacy of lansoprazole in this situation. Also since this is a subset of a larger study, it is difficult to draw firm conclusions about efficacy in special populations.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The applicant has demonstrated the safety of this combination package. Naproxen and lansoprazole are already approved as safe and efficacious. Naproxen is approved for over the counter use. Their combined use of naproxen and lansoprazole has already been approved in NDA20-406/S-33. A safety review of the pivotal trial M95-301 uncovered no safety concern. There is no evidence of a drug-drug interaction. In summary, the combination of postmarketing data, previous clinically trials, and the analysis from the study M95-301 all combine to establish safety for this combination package.

B. Description of Patient Exposure

The pivotal trial consisted of a total of 119 naproxen-only subjects in the study (30 subjects received placebo, 28 subjects received misoprostol, 37 subjects received lansoprazole 15 mg, and 24 subjects received lansoprazole 30 mg). The duration of the study was 12 weeks Table 3 previously displayed the duration of naproxen use among patients. The mean duration of naproxen use among patients was between 19 to 27 months for each treatment group. Table 4 shows the naproxen dose. The mean dosage ranged between 950 to 975 mg for the treatment groups.

C. Methods and Specific Findings of Safety Review

The study M95-301 was reviewed to assess safety. Naproxen and lansoprazole are already approved as safe and efficacious. Naproxen is approved for over the counter use. Their combined use has already been approved in NDA 20-406/S-33. Both medications are in widespread use worldwide. Thus, the safety review focuses on issues pertaining to the subset of patients on naproxen in the pivotal trial M95-301. The following table shows the treatment emergent events for each treatment arm during the study.

TABLE 9 - ALL TREATMENT EMERGENT ADVERSE EVENTS GROUPED BY BODY SYSTEM AND COSTART TERM FOR SUBJECTS WHO TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY

BODY SYSTEM/COSTART TERM $	PLACEBO (A) N= 30 MEAN EXPOSURE 51.6 DAYS N (PERCENT)	200 MCG QID MISOPROSTOL (B) N= 28 MEAN EXPOSURE 65.4 DAYS N (PERCENT)	15 MG QD LANSOPRAZOLE (C) N= 37 MEAN EXPOSURE 74.3 DAYS N (PERCENT)	30 MG QD LANSOPRAZOLE (D) N= 24 MEAN EXPOSURE 70.7 DAYS N (PERCENT)	P-VALUE@
TOTAL SUBJECTS					
ANY EVENT	15 (50.0)	18 (64.3)	20 (54.1)	13 (54.2)	
BODY AS A WHOLE					
ABDOMINAL PAIN	3 (10.0)	2 (7.1)	4 (10.8)	2 (8.3)	
ACCIDENTAL INJURY	2 (6.7)	1 (3.6)	0	0	
BACK PAIN	1 (3.3)	0	0	1 (4.2)	
CHEST PAIN	0	0	0	1 (4.2)	
FEVER	1 (3.3)	0	0	0	
FLU SYNDROME	0	3 (10.7)	1 (2.7)	0	
HALITOSIS	1 (3.3)	0	0	0	
HEADACHE	1 (3.3)	1 (3.6)	1 (2.7)	0	
HERNIA	0	0	0	1 (4.2)	
INFECTION	1 (3.3)	0	1 (2.7)	1 (4.2)	
PERITONITIS	1 (3.3)	0	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	8 (26.7)	6 (21.4)	7 (18.9)	3 (12.5)	
CARDIOVASCULAR SYSTEM					
ATRIAL FIBRILLATION	0	1 (3.6)	1 (2.7)	0	
CORONARY ARTERY DISORDER	0	0	0	1 (4.2)	
HYPERTENSION	0	0	1 (2.7)	0	
RETINAL VEIN THROMBOSIS	1 (3.3)	0	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	1 (3.3)	1 (3.6)	2 (5.4)	1 (4.2)	

$ SYMPTOMS WERE GROUPED BY COSTART TERMS
@ P-VALUE FOR PAIRWISE TREATMENT COMPARISIONS BETWEEN INDICATED TREATMENT GROUPS USING FISHER'S EXACT TEST
ONLY P-VALUES STATISTICALLY SIGNIFICANT AT 0.050 ARE PRESENTED

TABLE 9 – (Cont'd)

PLACEBO (A) N= 30	200 MCG QID MISOPROSTOL (B) N= 28	15 MG QD LANSOPRAZOLE (C) N= 37	30 MG QD LANSOPRAZOLE (D) N= 24

BODY SYSTEM/COSTART TERM $	MEAN EXPOSURE 51.6 DAYS N (PERCENT)	MEAN EXPOSURE 65.4 DAYS N (PERCENT)	MEAN EXPOSURE 74.3 DAYS N (PERCENT)	MEAN EXPOSURE 70.7 DAYS N (PERCENT)	P-VALUE@
DIGESTIVE SYSTEM					
CARDIOSPASM	0	1 (3.6)	0	0	
CONSTIPATION	0	1 (3.6)	0	0	
DIARRHEA	2 (6.7)	7 (25.0)	3 (8.1)	5 (20.8)	
DRY MOUTH	0	0	1 (2.7)	0	
DYSPEPSIA	0	1 (3.6)	1 (2.7)	0	
DYSPHAGIA	0	0	0	1 (4.2)	
ENTERITIS	0	0	1 (2.7)	0	
ESOPHAGITIS	0	1 (3.6)	1 (2.7)	0	
FLATULENCE	1 (3.3)	1 (3.6)	0	0	
GASTROENTERITIS	0	1 (3.6)	0	0	
INCREASED APPETITE	0	1 (3.6)	0	0	
INCREASED SALIVATION	1 (3.3)	0	0	0	
MELENA	1 (3.3)	0	0	0	
MOUTH ULCERATION	0	0	1 (2.7)	0	
NAUSEA	1 (3.3)	1 (3.6)	1 (2.7)	1 (4.2)	
RECTAL DISORDER	1 (3.3)	1 (3.6)	0	0	
TOOTH DISORDER	1 (3.3)	1 (3.6)	0	0	
VOMITING	0	1 (3.6)	1 (2.7)	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	5 (16.7)	13 (46.4)	8 (21.6)	7 (29.2)	
METABOLIC AND NUTRITIONAL DISORDERS					
EDEMA	0	0	1 (2.7)	0	
HYPERCHOLESTEREMIA	0	1 (3.6)	1 (2.7)	0	
PERIPHERAL EDEMA	1 (3.3)	0	1 (2.7)	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	1 (3.3)	1 (3.6)	3 (8.1)	0	

$ SYMPTOMS WERE GROUPED BY COSTART TERMS
@ P-VALUE FOR PAIRWISE TREATMENT COMPARISIONS BETWEEN INDICATED TREATMENT GROUPS USING FISHER'S EXACT TEST
ONLY P-VALUES STATISTICALLY SIGNIFICANT AT 0.050 ARE PRESENTED

TABLE 9 – (Cont'd)

BODY SYSTEM/COSTART TERM $	PLACEBO (A) N= 30 MEAN EXPOSURE 51.6 DAYS N (PERCENT)	200 MCG QID MISOPROSTOL (B) N= 28 MEAN EXPOSURE 65.4 DAYS N (PERCENT)	15 MG QD LANSOPRAZOLE (C) N= 37 MEAN EXPOSURE 74.3 DAYS N (PERCENT)	30 MG QD LANSOPRAZOLE (D) N= 24 MEAN EXPOSURE 70.7 DAYS N (PERCENT)	P-VALUE@

MUSCULOSKELETAL SYSTEM				
ARTHRALGIA	0	0	1 (2.7)	0
ARTHROSIS	0	0	1 (2.7)	0
BURSITIS	0	0	1 (2.7)	0
JOINT DISORDER	0	1 (3.6)	0	0
MYALGIA	0	1 (3.6)	1 (2.7)	0
TENDON DISORDER	0	0	1 (2.7)	0
SUBJECTS WITH ONE OR MORE SYMPTOMS	0	1 (3.6)	4 (10.8)	0
NERVOUS SYSTEM				
ANXIETY	0	1 (3.6)	2 (5.4)	0
DIZZINESS	0	1 (3.6)	0	2 (8.3)
HYPERTONIA	0	0	2 (5.4)	0
INSOMNIA	0	1 (3.6)	0	0
SUBJECTS WITH ONE OR MORE SYMPTOMS	0	2 (7.1)	4 (10.8)	2 (8.3)
RESPIRATORY SYSTEM				
BRONCHITIS	1 (3.3)	0	2 (5.4)	0
PHARYNGITIS	0	2 (7.1)	2 (5.4)	1 (4.2)
PLEURAL EFFUSION	0	0	1 (2.7)	0
PNEUMONIA	1 (3.3)	0	0	0
RESPIRATORY DISORDER	0	1 (3.6)	0	0
RHINITIS	0	0	1 (2.7)	0
SINUSITIS	0	0	1 (2.7)	1 (4.2)
SUBJECTS WITH ONE OR MORE SYMPTOMS	2 (6.7)	3 (10.7)	5 (13.5)	2 (8.3)

$ SYMPTOMS WERE GROUPED BY COSTART TERMS
@ P-VALUE FOR PAIRWISE TREATMENT COMPARISIONS BETWEEN INDICATED TREATMENT GROUPS USING FISHER'S EXACT TEST
ONLY P-VALUES STATISTICALLY SIGNIFICANT AT 0.050 ARE PRESENTED

TABLE 9 – (Cont'd)

BODY SYSTEM/COSTART TERM $	PLACEBO (A) N= 30 MEAN EXPOSURE 51.6 DAYS N (PERCENT)	200 MCG QID MISOPROSTOL (B) N= 28 MEAN EXPOSURE 65.4 DAYS N (PERCENT)	15 MG QD LANSOPRAZOLE (C) N= 37 MEAN EXPOSURE 74.3 DAYS N (PERCENT)	30 MG QD LANSOPRAZOLE (D) N= 24 MEAN EXPOSURE 70.7 DAYS N (PERCENT)	P-VALUE@
SKIN AND APPENDAGES					
FURUNCULOSIS	0	0	0	1 (4.2)	
RASH	0	0	1 (2.7)	1 (4.2)	
SKIN DISORDER	1 (3.3)	1 (3.6)	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	1 (3.3)	1 (3.6)	1 (2.7)	2 (8.3)	

SPECIAL SENSES				
TASTE LOSS	0	0	0	1 (4.2)
SUBJECTS WITH ONE OR MORE SYMPTOMS	0	0	0	1 (4.2)
UROGENITAL SYSTEM				
ACUTE KIDNEY FAILURE	0	0	1 (2.7)	0
BREAST CARCINOMA	0	0	1 (2.7)	0
BREAST NEOPLASM	0	0	1 (2.7)	0
BREAST PAIN	0	0	1 (2.7)	0
DYSURIA	0	1 (3.6)	0	0
HEMATURIA	1 (3.3)	0	0	0
PROSTATIC DISORDER	0	1 (3.6)	1 (2.7)	0
URINARY TRACT INFECTION	0	3 (10.7)	0	0
SUBJECTS WITH ONE OR MORE SYMPTOMS	1 (3.3)	5 (17.9)	4 (10.8)	0

$ SYMPTOMS WERE GROUPED BY COSTART TERMS
@ P-VALUE FOR PAIRWISE TREATMENT COMPARISIONS BETWEEN INDICATED TREATMENT GROUPS USING FISHER'S EXACT TEST
ONLY P-VALUES STATISTICALLY SIGNIFICANT AT 0.050 ARE PRESENTED

(Reference: Applicant electronic submission, Table 9, page 115)

The following table displays the most frequently reported treatment emergent adverse events.

TABLE 10- MOST FREQUENTLY REPORTED[a] TREATMENT-EMERGENT ADVERSE EVENTS BY TREATMENT GROUP AND DOSE AMONG NAPROXEN-ONLY SUBJECTS DURING THE RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER STUDY

	Treatment Group % (n)			
Body System/ COSTART Term	**Placebo (N=30)**	**Misoprostol 200 µg QID (N=28)**	**Lansoprazole 15 mg QD (N=37)**	**Lansoprazole 30 mg QD (N=24)**
Body as a Whole				
Abdominal Pain	10% (3)	7% (2)	11% (4)	8% (2)
Flu Syndrome	0	11% (3)	3% (1)	0
Accidental Injury	7% (2)	4% (1)	0	0
Digestive System				
Diarrhea	7% (2)	25% (7)	8% (3)	21% (5)
Nervous System				
Anxiety	0	4% (1)	5% (2)	0
Dizziness	0	4% (1)	0	8% (2)
Hypertonia	0	0	5% (2)	0
Respiratory System				
Bronchitis	3% (1)	0	5% (2)	0
Pharyngitis	0	7% (2)	5% (2)	4% (1)
Urogenital System				
Urinary Tract Infection	0	11% (3)	0	0

[a] Reported by =5% of subjects in any treatment group.
(Reference Table 5.4a, Electronic submission, page 23)

Medical Officer Comments: *There were no significant differences among the four treatment groups with respect to the incidence of any treatment-emergent adverse event.*

The following table shows the treatment related adverse events.

TABLE 11 – ALL POSSIBLY OR PROBABLY TREATMENT- RELATED ADVERSE EVENTS BY BODY SYSTEM AND COSTART TERM FOR SUBJECTS WHO TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY

BODY SYSTEM/COSTART TERM $	PLACEBO (A) N= 30 MEAN EXPOSURE 51.6 DAYS N (PERCENT)	200 MCG QID MISOPROSTOL (B) N= 28 MEAN EXPOSURE 65.4 DAYS N (PERCENT)	15 MG QD LANSOPRAZOLE (C) N= 37 MEAN EXPOSURE 74.3 DAYS N (PERCENT)	30 MG QD LANSOPRAZOLE (D) N= 24 MEAN EXPOSURE 70.7 DAYS N (PERCENT)	P-VALUE@
TOTAL SUBJECTS					
ANY EVENT	4 (13.3)	7 (25.0)	2 (5.4)	3 (12.5)	0.032* B VS C
BODY AS A WHOLE					
ABDOMINAL PAIN	2 (6.7)	1 (3.6)	0	1 (4.2)	
HALITOSIS	1 (3.3)	0	0	0	
HEADACHE	1 (3.3)	0	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	4 (13.3)	1 (3.6)	0	1 (4.2)	
DIGESTIVE SYSTEM					
CARDIOSPASM	0	1 (3.6)	0	0	
DIARRHEA	1 (3.3)	5 (17.9)	1 (2.7)	2 (8.3)	
DRY MOUTH	0	0	1 (2.7)	0	
FLATULENCE	1 (3.3)	1 (3.6)	0	0	
INCREASED APPETITE	0	1 (3.6)	0	0	
INCREASED SALIVATION	1 (3.3)	0	0	0	
NAUSEA	1 (3.3)	1 (3.6)	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	1 (3.3)	7 (25.0)	2 (5.4)	2 (8.3)	
NERVOUS SYSTEM					
DIZZINESS	0	1 (3.6)	0	0	
SUBJECTS WITH ONE OR MORE SYMPTOMS	0	1 (3.6)	0	0	
SPECIAL SENSES					
TASTE LOSS	0	0	0	1 (4.2)	
SUBJECTS WITH ONE OR MORE SYMPTOMS	0	0	0	1 (4.2)	

$ SYMPTOMS WERE GROUPED BY COSTART TERMS
@ P-VALUE FOR PAIRWISE TREATMENT COMPARISIONS BETWEEN INDICATED TREATMENT GROUPS USING FISHER'S EXACT TEST
ONLY P-VALUES STATISTICALLY SIGNIFICANT AT 0.050 ARE PRESENTED
*,**,*** STATISTICALLY SIGNIFICANT AT P= 0.05, 0.01, 0.001 LEVELS, RESPECTIVELY

(Reference: Applicant electronic submission, Table 8, page 109)

TABLE 12 - MOST FREQUENTLY REPORTED [a] POSSIBLY/PROBABLY TREATMENT-RELATED ADVERSE EVENTS BY TREATMENT GROUP AND DOSE AMONG NAPROXEN-ONLY SUBJECTS DURING THE RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER STUDY

Body System/ COSTART Term	Treatment Group % (n)			
	Placebo (N=30)	**Misoprostol 200 µg QID (N=28)**	**Lansoprazole 15 mg QD (N=37)**	**Lansoprazole 30 mg QD (N=24)**
Body as a Whole Abdominal Pain	7% (2)	4% (1)	0	4% (1)
Digestive System Diarrhea	3% (1)	18% (5)	3% (1)	8% (2)

[a] Reported by ≥5% of patients in any treatment group.

Medical Officer Comments: *The lansoprazole 15 mg group had statistically significantly fewer possibly or probably treatment-related adverse events reported compared to the misoprostol group (p = 0.032). Possibly or probably treatment related adverse events occurred in 5.4% of 37 subjects given lansoprazole 15 mg, 12.5% of 24 subjects given lansoprazole 30 mg, 25.0% of 28 subjects given misoprostol and 13.3% of 30 subjects given placebo. Only two of the 37 subjects given lansoprazole 15 mg had adverse events considered by individual investigators to be possibly or probably treatment-related.(one case each of diarrhea and dry mouth).*

The following table displays the serious adverse events among the patients who took lansoprazole

TABLE 13 - SUBJECTS ON LANSOPRAZOLE WHO HAD SERIOUS ADVERSE EVENT(S) AND TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY

TREATMENT* INVESTIGATOR	PAT. NO.	AGE SEX	DAYS OF TREAT-MENT	RX DAY TIME OF ONSET	RX DAY STOPPED (CONT.?)	ADVERSE EVENT(S)	SEVERITY	RELATION-SHIP	REASON SERIOUS DEA?	CAN?	CA?	HOS >23?	PD?	LT?
LANSOPRAZOLE 15 MG QD														
BREITER (8647)	5007	78M	42	33	51	ABDOMINAL PAIN	MODERATE	NO				YES		
STRONG (11339)	5265	62F	56	28	252	BREAST CARCINOMA	SEVERE	NO		YES		YES		
				16	35	BREAST NEOPLASM	MODERATE	NO		YES				
LANSOPRAZOLE 30 MG QD														
SAFDI (8515)	5194	69M	32	21	43	CORONARY ARTERY DISORDER	SEVERE	NO				YES		YES

* TREATMENT RECEIVED AT THE TIME OF OR IMMEDIATELY PRIOR TO THE ADVERSE EVENT START DATE
\# DEATH OCCURRED DURING POSTTREATMENT PERIOD
DEA=DEATH, CAN=CANCER, CA=CONGENITAL ANOMALY, HOS>23=HOSPITALIZATION >23 HOURS OR PROLONGATION OF HOSPITALIZATION, PD=PERMANENT DISABILITY, LT=LIFE THREATENING

(Reference: Electronic submission, Table 11, page 124)

Medical Officer Comments: *The case report forms for the severe adverse events were reviewed. None of these events appeared related to lansoprazole. Patient 5007 suffered an intraabdominal abscess that required hospitalization that had no relation to either of the study drugs.*

TABLE 14- SUBJECTS ON LANSOPRAZOLE WHO PREMATURELY DISCONTINUED DUE TO ADVERSE EVENT(S) AND TOOK NAPROXEN ONLY OR NAPROXEN AND ASPIRIN ONLY

TREATMENT GROUP	INVESTIGATOR	SUBJECT NUMBER	AGE SEX	DAYS OF TREATMENT	REASON(S) FOR TERMINATION ADVERSE EVENT(S) (SEVERITY, RELATIONSHIP)
LANSOPRAZOLE 15 MG QD					
	BREITER (8647)	5007	78M	42	#ADVERSE EVENT - ATRIAL FIBRILLATION (SEVERE, NO RELATIONSHIP)
	STRONG (11339)	5265	62F	56	#ADVERSE EVENT - BREAST CARCINOMA (SEVERE, NO RELATIONSHIP)
LANSOPRAZOLE 30 MG QD					
	SAFDI (8515)	5194	69M	32	#ADVERSE EVENT - CORONARY ARTERY DISORDER (SEVERE, NO RELATIONSHIP)
	SILVERS (4261)	5152 @	56M	10	OTHER - PATIENT STARTED EXCLUSIONARY DRUG COUMADIN #ADVERSE EVENT - BACK PAIN (MODERATE, NO RELATIONSHIP), CHEST PAIN (MILD, NO RELATIONSHIP), DIZZINESS (MILD, RELATIONSHIP) THERAPEUTIC FAILURE

@ SUBJECT EXCLUDED FROM PRIMARY EFFICACY ANALYSES OF EVALUABLE SUBJECTS
# PRIMARY REASON

(Reference: Electronic submission, Table 11, page 124)

Medical Officer Comments: *None of the adverse events that led to withdrawals were related to the study drug.*

D. Adequacy of Safety Testing

The safety data submitted by the sponsor is adequate. Both naproxen and lansoprazole are previously approved agents in widespread use. Consequently, large clinical trials and postmarketing data have been previously evaluated by the Agency and deemed to demonstrate safety. The safety review of clinical trial M95-301 although containing a small number of patients is adequate in conjunction with previous data.

E. Summary of Critical Safety Findings and Limitations of Data

The applicant has demonstrated these agents are safe to use together. In a well controlled trial (albeit one with a small number of patients) the subjects who took naproxen and lansoprazole had a similar number of adverse events versus placebo and the active control. The subjects in the 15 mg lansoprazole arm had statistically fewer adverse events when compared to misoprostol. The data is limited in that in lieu of a large well controlled trial the applicant has submitted an analysis of a subset of patients. However, it should be noted that both naproxen and lansoprazole are have been previously approved as safe. It is possible that two agents which are safe separately can have untoward effects when used together. However both these medications are in widespread use and postmarketing data does not reveal any increase in adverse events when they are used together. In addition, there currently exists no biological basis for a potential increase in adverse events when used together. In summary, the combination of postmarketing data, previous clinical trials, and the analysis from the study M95-301 all combine to establish safety.

VIII. Dosing, Regimen, and Administration Issues

The applicant is proposing a combination package of four 7-day blister cards containing two naproxen tablets (either 250 mg, 375 mg or 500 mg strengths) and 15 mg lansoprazole capsule. The naproxen is to be taken twice a day, and the lansoprazole is to be taken in the morning. The advantage of the combination package is it allows for a single prescription and likely will improve compliance. Patients who may be less likely to remember to take medications individually may be more adherent if they are packaged together. Combination packaging has the disadvantage of limiting individual dose titration. However, by including various doses with the lansoprazole 15 mg there may be some flexibility in dosing. Seventy-five percent of naproxen users take 500 mg BID and 90% of naproxen prescriptions are written for the 375 mg and 500 mg strengths. It should be noted that the study had few patients who took a dose greater than 1000 mg of naproxen. Therefore, the labeling should reflect the lack of data to support the efficacy of lansoprazole when the dose of naproxen is greater than 1000 mg.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The applicant did not submit any new data regarding gender effects. The study M95-301 was comprised of 73 (61.3%) female and 46 (38.7%) male patients. The efficacy data was broken down by gender and revealed at the end of week 12, 89% of females and 88% of males receiving lansoprazole 15 mg were gastric ulcer-free. In contrast, 41% of females and 20% of males were ulcer free in the placebo group. Thus, there did not appear to be any difference in

efficacy based on gender. There also was no significant difference in safety profile between male and female patients.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The applicant did not submit new data concerning the effect of age or race on safety or efficacy. The mean age of the patients in study M95-301 was 59.5 years with a range of 37 to 84 years. An analysis was performed comparing the efficacy of patients under 65 years of age to those over 65. This analysis showed that a higher proportion of lansoprazole patients of both age groups remained gastric ulcer-free by week 12 as compared to the placebo group. The safety data from study M95-301 did not reveal any issues particular to the geriatric population. There are no specific safety issues regarding lansoprazole use in the elderly. However, the clearance of lansoprazole is decreased in the geriatric population. The naproxen label relates no safety issues in the elderly; however it is well known that patients over the age of 60 years are at higher risk of gastrointestinal complications from NSAIDs. In summary, when used individually and collectively both naproxen and lansoprazole are safe and effective in the elderly.

The subset of patients on naproxen in study M95-301 was comprised of the following racial groups:

- 105 (88.2%) Caucasian patients
- 9 (7.6%) Black patients
- 5 (4.2%) Other

Because of these relatively small numbers, a subgroup analysis with respect to race was not performed. The current lansoprazole label states that Asians have an increase in the AUC when compared to patients in the U.S. However, since the approval of lansoprazole no safety or efficacy differences in various ethnic subgroups have come to light. The current naproxen label does not relate any issues with regard to use in different races.

C. Evaluation of Pediatric Program

The applicant currently has no plans to pursue a pediatric indication. Chronic NSAID use and NSAID induced gastric ulcers are less common in the pediatric population. Due to the small numbers involved, there are currently no plans to request pediatric studies pertaining to this indication in the Agency's Written Request for proton pump inhibitors.

D. Comments on Data Available or Needed in Other Populations

These agents are already approved and widely used in multiple subgroups. The current label for lansoprazole provides data on use in patients with hepatic and renal insufficiency. The current label for naproxen states that pharmacokinetics have not been determined in subjects with renal insufficiency and cautions on the use in patients with impaired hepatic function. At this time, no further data is needed in other populations.

X. Conclusions and Recommendations

A. Conclusions

The applicant's submission demonstrates a favorable risk/benefit profile for this indication. Efficacy is based on an analysis of a subset of patients on naproxen and lansoprazole in clinical study M95-301. In this study lansoprazole demonstrated a statistically significant risk reduction of NSAID-associated gastric ulcer compared to placebo. Safety is established by a

combination of postmarketing data, previous clinical trials, and the analysis from the study M95-301. This data when taken together establishes safety for use of these medications jointly.

Study M95-301 was previously reviewed and judged to demonstrate the efficacy of lansoprazole versus placebo in healing and risk reduction of NSAID-associated gastric ulcers while continuing NSAID treatment. In support of this combination package, TAP has submitted a subset analysis of naproxen only subjects. The results of this analysis demonstrate that lansoprazole is statistically significantly more effective than placebo in reducing the risk of NSAID-associated gastric ulcer in subjects who continue the use of NSAID therapy ($p \leq 0.001$). Lansoprazole also demonstrated significantly less severe and a significantly smaller percentage of days with daytime and nights with nighttime abdominal pain than misoprostol-treated subjects. Patients in the lansoprazole arms had less use of antacids as well. In addition it does not appear that lansoprazole interfered with the efficacy of naproxen. There were no statistically significant differences observed among any of the treatment groups for the percentage of days or average pain severity of day or night joint pain/swelling.

The applicant has demonstrated these agents are safe to use together. In a well controlled trial the subjects who took naproxen and lansoprazole had a similar number of adverse events versus placebo and the active control. The subjects in the 15 mg lansoprazole arm had statistically fewer adverse events when compared to misoprostol. The data is limited in that in lieu of a large well controlled trial the applicant has submitted an analysis of a subset of patients. However, it should be noted that both naproxen and lansoprazole have been previously approved as safe. Both these medications are in widespread use and postmarketing data does not reveal any increase in adverse events when they are used together. In addition, there currently exists no biological basis for a potential increase in adverse events when used together. In summary, the combination of postmarketing data, previous clinical trials, and the analysis form the study M95-301 all combine to establish safety.

B. Recommendations

There are two issues regarding this NDA. Firstly, the applicant has not submitted a formal study to evaluate the interaction between naproxen and lansoprazole, but instead has chosen to rely on a literature review involving drugs in the same class and extrapolate the results to these two medications. It should be noted that naproxen is an over the counter medication and has a wide therapeutic window. However, it could be argued that co-packaging these two medications together requires a higher standard for evaluation of drug interactions and a Phase 4 Study to fully evaluate the interaction between lansoprazole and naproxen should be considered. Secondly, it should be noted that few patients took a dose of naproxen greater than 1000 mg. Therefore, the labeling should reflect the lack of data to support the efficacy of lansoprazole when the dose of naproxen is greater than 1000 mg.

XI. Appendix

A. References

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